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INVITED REVIEW

Mechanisms of Blood-Brain Barrier Disruption in Herpes Simplex Encephalitis

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Abstract

Herpes simplex encephalitis (HSE) is often caused by infection with herpes simplex virus 1 (HSV-1), a neurotropic double-stranded DNA virus. HSE infection always impacts the temporal and frontal lobes or limbic system, leading to edema, hemorrhage, and necrotic changes in the brain parenchyma. Additionally, patients often exhibit severe complications following antiviral treatment, including dementia and epilepsy. HSE is further associated with disruptions to the blood-brain barrier (BBB), which consists of microvascular endothelial cells, tight junctions, astrocytes, pericytes, and basement membranes. Following an HSV-1 infection, changes in BBB integrity and permeability can result in increased movement of viruses, immune cells, and/or cytokines into the brain parenchyma. This leads to an enhanced inflammatory response in the central nervous system and further damage to the brain. Thus, it is important to protect the BBB from pathogens to reduce brain damage from HSE. Here, we discuss HSE and the normal structure and function of the BBB. We also discuss growing evidence indicating an association between BBB breakdown and the pathogenesis of HSE, as well as future research directions and potential new therapeutic targets.

Keywords Herpes simplex encephalitis · Blood-brain barrier · Tight junctions · Microglia · Immune response

Background

Herpes Simplex Encephalitis

Herpes simplex virus 1 is the most common and invasive pathogen, existing in at least 70% of humans worldwide, usually acquired from intimate contact with family in early childhood (Whitley 2006). Rates of HSV-1 infection are similar for women and men. It is a neurotropic virus that always initially infects peripheral mucosal sites, leading to herpes labialis. Following the primary infection, the virus remains latent in nervous system including the trigeminal ganglia and the olfactory bulbs, establishing a lifelong latent infection (Feldman 2002; Shivkumar et al. 2013). In these latent cases, the viral genome is present even when no virion is present.

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The mechanisms by which HSV-1 gains access to the central nervous system (CNS) remain unclear. The most likely routes include retrograde transport via the olfactory or trigeminal nerve fibers into the CNS, occasionally leading to herpes simplex encephalitis (HSE) (Davis and Johnson 1979; Esiri 1982; Jennische et al. 2015). HSE is the most common sporadic encephalitis worldwide, with over 90% of cases caused by the herpes simplex virus type-1 (HSV-1) and approximately 7% by HSV-2 (Hjalmarsson et al. 2007). When compared to HSV-1, HSV-2 can also cause brain infections in young adult women, mainly HSV-2 meningitis (HSM) and women are six times more likely to develop HSM compared to men (Read and Kurtz 1999; Yechiel Schlesinger and Storch 1995). It is self-limited and usually not associated with permanent neurologic sequel (Lind et al. 2017). Meanwhile, these differ in their ability to reactivate viral materials in the trigeminal and dorsal root ganglia. Reactivation in the lumbar-sacral ganglia is more efficient, resulting in disease below the waist, including in the genitalia (Margolis et al. 2007).

Manifestations of HSE include encephalopathy, fever, seizures, headaches, and focal neurological deficits (Bradshaw and Venkatesan 2016). Without therapy, the mortality of HSE reaches up to 70% in patients. Using antiviral therapy, the mortality can be reduced to 20–30% (Simko et al. 2002;

Saraya et al. 2016). HSE survivors exhibit varying degrees of cognitive, memory, and behavioral deficits despite antiviral therapy. Previous data have shown that over two-thirds of HSE cases result from viral reactivation (Steiner 2011). Specifically, brain damage is mediated by the direct lytic effects of the virus on neurons and glia, as well as often significant neuroinflammatory responses (Lokensgard et al. 2002; Lundberg et al. 2008a; Sellner et al. 2005; Zhou et al. 2016a). It is also well-established that the permeability and integrity of the blood-brain barrier (BBB) is compromised in HSE (Stroop et al. 1990). This leads to vasogenic brain edema, hemorrhage, leukocyte infiltration, and progressive inflammation that induces brain damage and is accompanied by cerebral microcirculation and metabolic disturbances (Taskinen et al. 1984).

Components of the Blood-Brain Barrier

The BBB serves as an interface between the brain parenchyma and systemic circulation. It controls the entry of nutrients, vitamins, ions, and other molecules into the brain to protect it from harmful materials, such as toxins and pathogens (Daneman and Prat 2015; Spindler and Hsu 2012). The BBB is composed of brain microvascular endothelial cells (ECs), tight junctions (TJs), astrocytes, pericytes, and the basal membrane (BM) (Abbott et al. 2010). Malfunctions in any of these components can lead to critical changes in the BBB's functions (Fig. 1).

Endothelial Cells

ECs are the primary components of the BBB and have a low rate of pinocytosis, lack fenestrations, and have a higher mitochondrial content than peripheral vascular endothelial cells. The special structure of the BBB is determined by the special functions of ECs (Almutairi et al. 2016). Under normal physiological conditions, low expression of intracellular adhesion molecule 1 (ICAM-1) on ECs limits the entry of immune cells into the CNS (Albert et al. 1995). The low permeability and integrity of ECs is a prerequisite for their protection of the CNS from harmful bloodborne materials. Critically, the barrier function of the BBB is altered in most CNS pathologies. For instance, in HSE, ECs may be disrupted by several different factors.

Tight Junctions

TJs are located between ECs and include both TJ and adhesion junction (AJ) proteins (Stamatovic et al. 2016). The integrity of TJs is a prerequisite for the maintenance of normal BBB functions. It is thought that TJ proteins seal clefts between endothelial cells while AJ proteins maintain and regulate the interactions between these cells (L. Gonzalez-Mariscal 2003).

TJ proteins fall into two main categories: transmembrane, such as claudins-3, −5, and − 12, and occludin, and cytoplasmic, such as zonula occluden 1, 2, and 3 (ZO-1, ZO-2, and ZO-3) (Haseloff et al. 2015). Previous studies have shown that ECs predominantly express claudin-3 and claudin-5 (Morita et al. 1999; Wolburg et al. 2003). Occludin is composed of four transmembrane domains, with carboxyl and amino terminals oriented towards the cytoplasm and two extracellular loops spanning the intercellular clefts. Cytoplasmic proteins link these transmembrane proteins to the actin cytoskeleton (Broux et al. 2015). For example, ZO-1, which was the first accessory protein to be identified, links occludin to the actin cytoskeleton and thus plays a pivotal role in regulating the permeability of the BBB (Fanning 2002). The actin cytoskeleton in brain ECs is not the traditional protein in TJs, but plays a critical role in regulating BBB permeability (Lai et al. 2005).

Cytoskeletal protein expression and distribution in the BBB under different circumstances, including HSE, regulates the molecular structure and function of TJ proteins. TJs can promote and maintain high transendothelial electrical resistance (TEER) in the BBB (Thomsen et al. 2015). This, in turn, restricts the free flow of ions and solutes and reduces paracellular permeability. In pathological conditions, damage to ECs or alterations in TJs can lead impaired integrity and/or permeability of the BBB.

Astrocytes

Astrocytic endfeet in the brain cover more than 99% of the cerebral vasculature and serve as exchange sites for ions, metabolites, and energy substrates between the blood and the brain (Mathiisen et al. 2010). Astrocytes may contribute to the unique properties of ECs and impermeability of the BBB (Abbott 2002). In line with this, astrocyte-endothelial co-culture models of the BBB have higher TEER and lower permeability than the model composed only of ECs (Wang et al. 2015a, b). In addition, studies have demonstrated that astrocytes regulate the integrity and permeability of the BBB by releasing soluble factors, such as vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) (Argaw et al. 2012; Chapouly et al. 2015). The normal function of astrocytes is thus necessary for the maintenance of the unique characteristics of the BBB. As such, astrocytic malfunctions often lead to BBB damage.

Pericytes and the Basement Membrane

Pericytes are adjacent to capillaries and share a common BM with ECs. Together with ECs and astrocytes, they are essential to the regulation and restriction of the transport of various materials (Armulik et al. 2010).

Via contacts with ECs and the release of soluble substances, such as PDGF-Rβ and transforming growth factor-

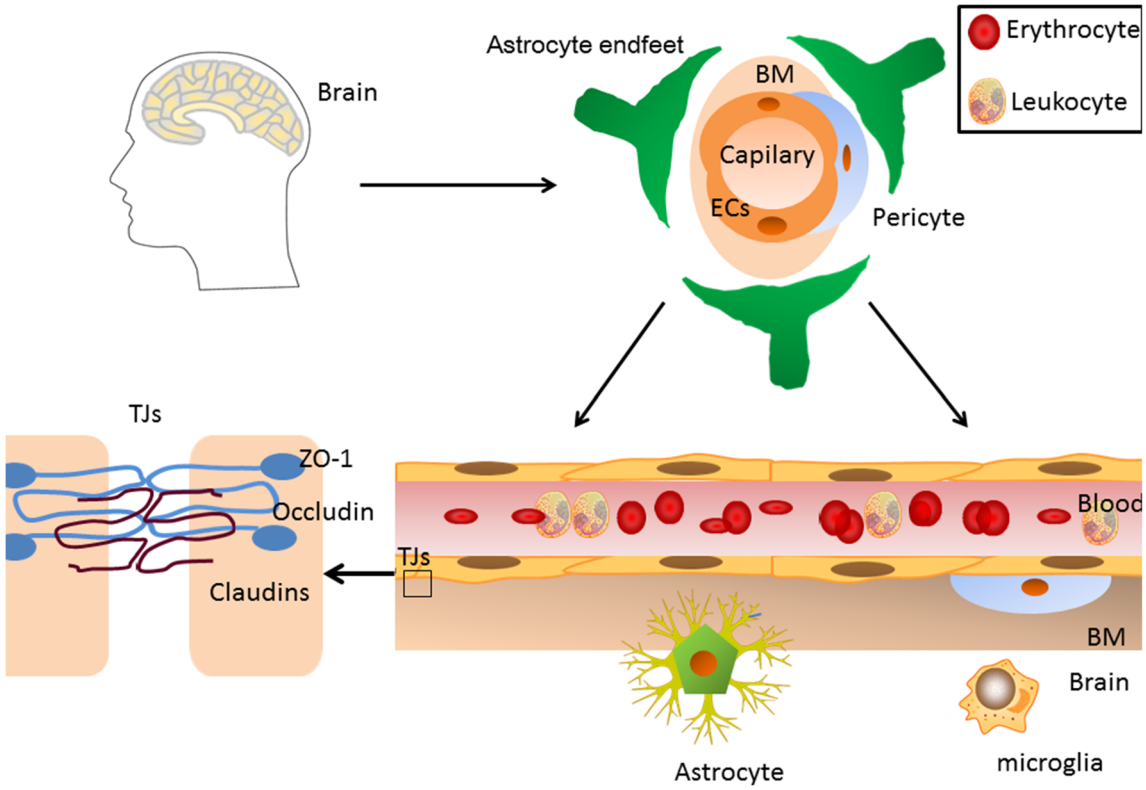

Fig. 1 Components of the blood-brain barrier (BBB). The BBB is composed of ECs, astrocyte endfeet, pericytes, and BM. TJs, which are located between ECs, ensure a close association between adjacent cells. Microglia are the brain's resident immune cells and play additional, vital roles on protecting BBB function

beta (TGF-ß), pericytes can significantly deregulate the BBB permeability and enhance its functions (Dohgu et al. 2005; Hill et al. 2014). When compared with the EC-monolayer system, the endothelial-pericyte contact model exhibits tighter barrier function, suggesting that pericytes contribute to the integrity of the BBB (Hayashi et al. 2004).

The BM is another essential component of the BBB. It is primarily composed of a mixture of extracellular matrix (ECM) proteins, such as type IV collagen, laminin, and fibronectin (Hamann et al. 1995). The BM lies between ECs and pericytes, anchoring cells in place and providing connections with surrounding cells in the brain (Carvey et al. 2009). Disruption of the BM contributes to alteration in the EC cytoskeleton, which in turn leads to disruption of TJs. Matrix metalloproteases (MMPs) are well-known enzymes that digest ECM and thus impair BBB integrity (Di Cara et al. 2018).

Microglia

Microglia are the resident immune cells of the CNS. Traditionally, they are not considered to be a part of the BBB, though they play indispensable roles in regulating its integrity. Microglia exhibit two canonical states: resting, with a ramified morphology; and activated, with an amoeboid morphology (Block and Hong 2005). In the brain parenchyma, ramified microglia continually extend and retract their processes to sense changes in the surrounding microenvironment (Hanisch and Kettenmann 2007; Kreutzberg 1996). In general, microglia maintain brain immune homeostasis by triggering scavenging, phagocytosis, cytotoxicity, antigen presentation, and extracellular signaling processes. When an injury or disturbance to homeostasis occurs in the CNS, microglia become activated (Liu and Hong 2003). When activated, microglia move to the site of an injury, proliferate, and regulate the brain's adaptive immune response, such as immune cells recruitment, and cytokines release (Kettenmann et al. 2011).

Previous studies have identified microglia as the primary sources of pro-inflammatory cytokines and chemokines released in response to HSV-1 infection. These molecules include type I interferon (IFN), interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), chemokine (C-X-C motif) ligand 10, C-C motif chemokine ligand 2 (CCL2), and inducible NOS (iNOS) (Marques et al. 2008a, b; Lokensgard et al. 2001). Activated microglia also release molecules with anti-viral effects, such as IFN, via the cyclic guanosine monophosphate (cGMP)-adenosine monophosphate synthase (cGAS)–Stimulator of Interferon Genes (STING) pathway (Reinert et al. 2016). These molecules are protective against HSE when released in appropriate amounts. These inflammatory mediators also facilitate the migration of

peripheral immune cells into the CNS, aggravating the brain's immune response, thus leading to BBB disruptions. A growing number of studies have indicated the significance of microglia in CNS disease, with some studies specifically focusing on the regulation of microglial function in pathology (Zhou et al. 2016b).

Mechanisms and Related Factors of Blood-Brain Barrier Disruption in Herpes Simplex Encephalitis

Previous data have indicated that the BBB is disrupted in HSE, contributing to the development of multiple pathological processes such as vascular brain edema, hemorrhage, and leukocyte infiltration. These each leads to further brain damage and thus more serious severe clinical diseases. The structure and functions of the BBB are altered when it is disrupted. We will next discuss how various alterations in the BBB, including to each of its components, may pathological states, as well as potential therapeutic approaches that might be used to repair BBB structure and function.

Alterations in Brain Microvascular Endothelial Cells in Herpes Simplex Encephalitis

ECs, which form the barrier in the BBB, are often the most proximal targets of harmful circulating materials. The structure and function of ECs is altered following HSV-1 infection. These effects are mediated by changes in ICAM-1 and nitric oxide (NO) levels (Fig.2).

Intracellular Adhesion Molecule 1 (ICAM-1)

ICAM-1 is an intermembrane glycoprotein that belongs to the immunoglobulin superfamily. It is a ligand for LFA-1, which is a receptor on leukocytes (Dietrich 2002). ICAM-1 is expressed at the luminal surface of ECs, with an intercellular domain that has been shown to interact with cytoskeleton-associated proteins (Carpen et al. 1992). Under physiological conditions, ECs express low levels of ICAM-1. Many different factors, including viral or bacterial infection, immune factors, can markedly increase ICAM-1 expression (Lee et al. 2018; Kim et al. 2000; Dobbie et al. 1999). Previous research has shown that protein kinase C (PKC), which belongs to the serine/threonine kinase family, can induce the binding of nuclear factor kappa B (NF-κB) to the ICAM-1 promoter in a TNF-α-dependent manner, leading to ICAM-1 gene transcription (Rahman et al. 2000). Many diseases, including multiple sclerosis (MS) and meningitis, are characterized by the upregulation of ICAM-1 expression (Huang et al. 2017). Following HSV-1 infection, activated microglia secrete large amounts of cytokines, such as TNF-α, IL-1β, and IFN-γ, which can stimulate further ICAM-1 expression on the surface of ECs, as has been described above (Kim et al. 2000; Yuping ZHU 2013). Consistent with previous studies, the expression of ICAM-1 on ECs increases following HSV-1 infection (Brankin et al. 1995; Sobel et al. 1990). Lewandowski et al. further demonstrated that the mRNA expression of ICAM-1 significantly increases in an HSE mouse model relative to uninfected controls (Lewandowski and Hobbs 1998).

ICAM-1 determines the structure and function of the endothelial barrier and has been studied for its function in the regulation of leukocyte movement across ECs (Roe et al. 2014). The BBB limits the movement of perivascular cells into the CNS due to its low permeability and integrity under normal conditions. Given a healthy BBB, only a small number of leukocytes pass through the endothelial barrier, as it is impermeable to most molecules. HSV-1 infection, however, results in increased ICAM-1 expression and, as a result, increased leukocyte interaction with ECs via LFA-1/ICAM-1 binding. Peripheral leukocytes thus undergo adhesion, rolling, transmigration, and migration across the endothelial barrier and into the brain. This leads to an enhanced immune response in the brain, which triggers further brain parenchymal damage in viral-infected tissues (Lundberg et al. 2008b).

Recent evidence has also indicated that the cross-linking of ICAM-1 and LFA-1 increases intercellular calcium levels and leads to rearrangements in the cytoskeleton. Small guanosine triphosphate-binding proteins, such as Rho, also play vital roles in this process. The activation of Rho can induce the phosphorylation of three cytoskeleton-associated proteins: FAK, paxillin, and CAS. Alterations in the phosphorylation states of these proteins lead to changes in the ECs cytoskeleton, facilitating leukocyte trafficking (Etienne-Manneville et al. 2000; Peter Adamson et al. 1999). These alterations can influence the structure and permeability of the endothelial barrier, thus contributing to BBB disruption and indirectly to immune damage of the brain parenchyma. In addition, some studies have indicated that calcium chelators largely prevent leukocyte transmigration across endothelial cells. This finding suggests that leukocyte migration across the endothelium is dependent, at least in part, on calcium-signaling pathways (Clayton et al. 1998). Furthermore, calcium serves as a second messenger and thus plays important roles in cells, such as in the activation of calmodulin and eNOS, which in turn induce NO release and alter the normal functioning of endothelial cells (Shukla et al. 1995). Collectively, these findings provide compelling evidence in support of the idea that increased expression of ICAM-1 is a critical factor in BBB disruptions in HSE.

Nitric Oxide

NO is a free radical that plays an important role in primary defense mechanisms against many pathogens, including viruses. It inhibits viral replication and is thus protective following viral infection (Croen 1993). However, NO also has a

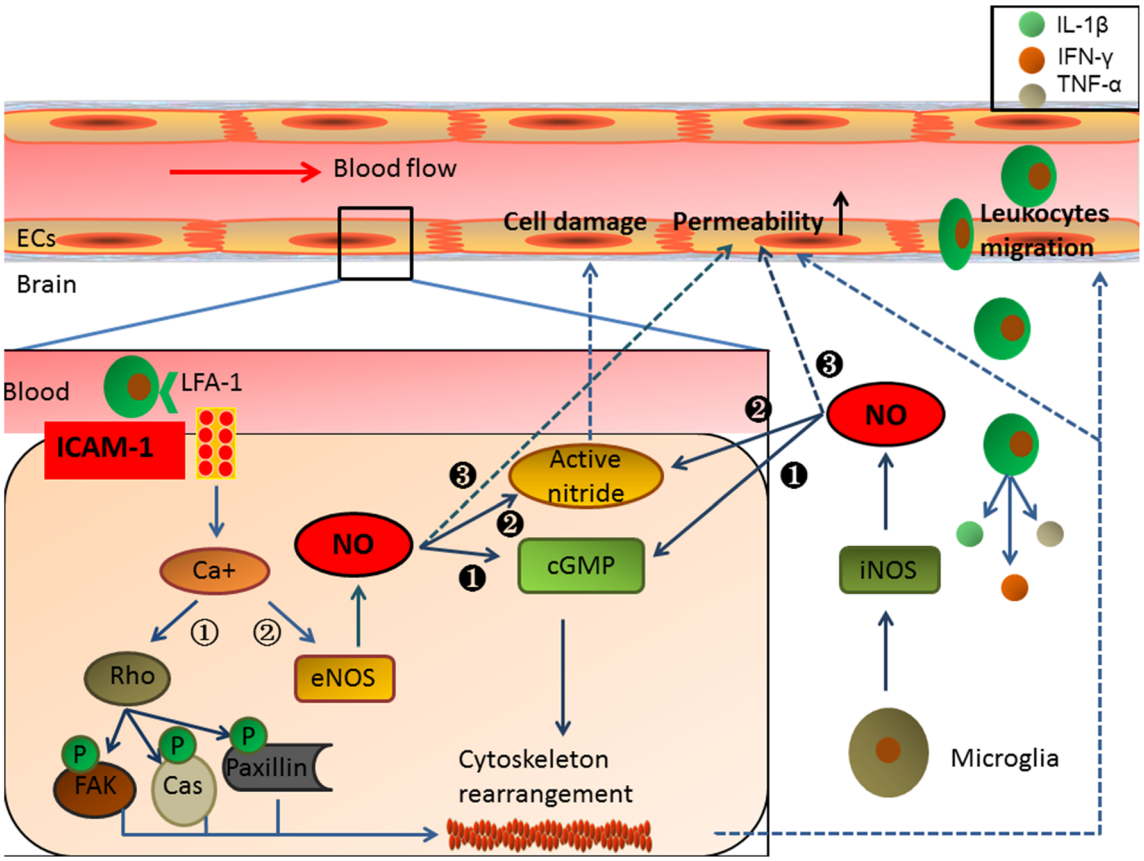

Fig. 2 The role of ICAM-1 and NO in disruptions to the blood-brain barrier. ***I.*** **ICAM-1**: Upregulated ICAM-1 and lymphocyte function-associated antigen 1 (LFA-1) together facilitate leukocyte migration and robust calcium release. These two molecules participate in endothelial barrier disruption via two mechanisms: ① induction of focal adhesion kinase (FAK)/Crk-associated substrate (CAS)/paxillin phosphorylation by Rho, which leads to cytoskeletal rearrangement; ② the release of calcium, which can stimulate the release of NO. In turn, NO can alter EC functions via three known mechanisms: ❶ induction of cytoskeleton rearrangement via cGMP activation, which facilitates the movement of immune cells from the blood into the brain and increases BBB permeability; ❷ formation of active nitride species, which can induce cell and tissue damage; and ❸ as a vasodilator, which increases BBB permeability

deleterious role in BBB functioning, as it can also aggravate inflammation and promote cytotoxicity when expressed at high levels. Accumulating evidence indicates that NO is involved in BBB disruption across various pathologies, such as epilepsy, intracerebral hemorrhage, and experimental autoimmune encephalomyelitis (EAE) (Ding et al. 2014; Ko et al. 2015a; Wu and Tsirka 2009).

Furthermore, NO is also unstable, with a half-life of only 3–4 s in the blood. Given this, researchers prefer to study NOS, which has three isoforms: eNOS, iNOS, and neuronal NOS (nNOS). nNOS promotes NO production by neurons, ECs, and macrophages, including activated microglia. eNOS and nNOS are calcium-dependent and are constitutively expressed, while iNOS is not calcium-dependent and is expressed in an inducible fashion.

Collectively, the literature suggests that NO leads to BBB damage via three main mechanisms. First, high levels of NO form highly active nitrides, such as peroxynitrite and nitrate, in the tissue. These molecules result in the production of nitrotyrosine, which causes lipid peroxidation and cell or tissue damage (Fujii et al. 1999). Second, NO is a vasodilator, regulating vascular tone and thus local blood flow, which can increase EC permeability and change normal BBB functions (Mark et al. 2004). A previous study found that the expression of iNOS mRNA is upregulated in both the early and late stages of HSV-1 infection. Mark et al. (2004) further speculated that iNOS might act as a mediator of secondary immune-mediated tissue damage (Meyding-Lamade et al. 1998).

Critically, some have also used an inhibitor of iNOS to successfully treat animal models of HSE, correcting its clinical symptoms and mortality. (Fujii et al. 1999; Meyding-Lamade et al. 2002). In addition, NO regulates BBB permeability via the NO signal transduction pathway because NO diffuses through cell membranes to activate soluble guanylyl cyclase, a cytoplasmic enzyme that produces cGMP. cGMP, in turn, regulates cGMP-dependent protein kinase (Wong et al. 2004). Critically, brain ECs express cGMP-dependent protein kinase, which is associated with the cytoskeleton, indirectly lead to BBB disruption by NO (Chen et al. 2003). These data provide compelling evidence that excessive NO production

following an HSV-1 infection may be an important factor in disruptions to the BBB with HSE, although elucidating the specific underlying mechanisms requires further research.

In summary, the structure and function of the EC barrier may be disrupted by varying actions of ICAM-1 and NO after HSV-1 infection.

Alterations in Tight Junction Proteins in Herpes Simplex Encephalitis

TJ proteins are the most important components of the BBB. Alterations to these proteins may lead to BBB disruptions. Critically, TJ proteins undergo degradation, phosphorylation, and redistribution during HSE (Fig. 3).

Matrix Metalloproteinases

MMPs are zinc-dependent endopeptidases that cleave TJ proteins and extracellular matrix proteins. Thus, the proteolytic activity of these proteins can directly lead to BBB disruption (Yang et al. 2007). MMPs are secreted as zymogens and must be cleaved to become fully active. Specifically, MMP2 and MMP9 have been carefully studied in the context of CNS disease and mounting evidence suggests that both play pivotal roles in BBB disruption, edema formation, and disintegration of the neurovascular unit. For example, MMP2 degrades claudin-5 and occludin in ischemic foci in a rat model of ischemic stroke. These effects are attenuated following administration of MMP2 inhibitors in the early phase of ischemia, when BBB disruption is reversible, indicating both the sufficiently and necessity of MMP2 for these effects (Yang et al. 2007). BBB disruption in mouse model of adenovirus type-1 encephalitis has been shown to be partly due to the increased activity of MMPs, including MMP2 and MMP9 (Ashley et al. 2017).

Disruptions to the BBB are also often accompanied by significant upregulation of MMP expression, both in patients with HSV-1 and in animal models (Martínez-Torres et al.

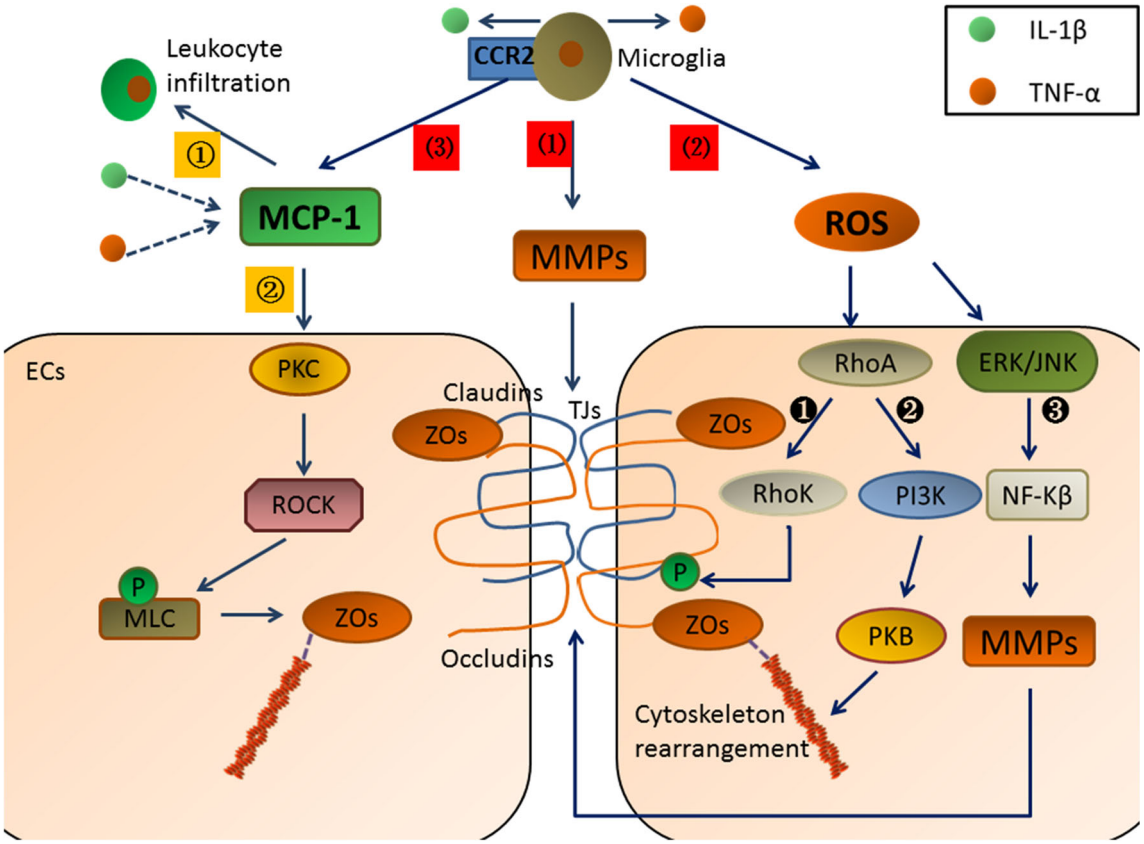

Fig. 3 Role of matrix metalloproteinases, reactive oxygen species, and monocyte chemoattractant protein 1 in disruption of the blood-brain barrier. 1) MMPs may disrupt TJs due to their endopeptidase activity. In addition, they cleave claudins, occludin, and ZO-1, which leads to BBB disruption. 2) ROS induces alterations in BBB integrity and permeability primarily via the following mechanisms: ❶ phosphorylation of TJ proteins via the RhoA/RhoK pathway; ❷ cytoskeletal rearrangement via the RhoA/phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) pathway; and ❸ regulation of the expression of MMPs by activating the extracellular signal-regulated kinase (ERK)/c-Jun N-terminal kinase (JNK)/NF-κB pathway, which indirectly affects BBB integrity. 3) MCP-1 also influences the BBB via two mechanisms: ① by attracting leukocytes from the blood into the brain parenchyma, which leads to an enhanced immune response in the brain, and ② via stimulating EC contraction, which in turn leads to the movement of ZO-1 away from TJs via the protein kinase C (PKC)/Rho-kinase (ROCK)/myosin light chain kinase pathway and thus indirect disruption of BBB integrity

2004; Sellner et al. 2006). Previous studies in patients with viral meningitis have indicated that MMP expression markedly increased in the CSF (Kolb et al. 1998). For instance, Zhou et al. reported significant increases in MMP2 and, to an even greater degree, MMP9 levels in a mouse model of HSE. These increases were accompanied by disruptions to the integrity of the BBB (Zhou et al. 2010). MMP9 has further been shown to be primarily expressed in OX-42-positive cells, indicating that activated microglia may be the main source of MMP9 (Zhou et al. 2016a). Furthermore, small interfering RNAs against MMP9 and MMP2 or MMP9 inhibitors reduce damage to the BBB (Feng et al. 2011). Studies also indicate that TJ proteins contain MMP cleavage sites, the activation of which leads to TJ proteins cleavage and detachment of ECs from the ECM, which is a critical step in BBB disruption (Cummins 2011). These data provide compelling evidence that MMPs are important factors in BBB disruption, as they promote the degradation of TJ proteins in HSE.

Reactive Oxygen Species

ROS, which are generated by intracellular metabolic processes, both benefit the clearance of pathogens and also result in secondary damage to the brain in HSE (Milatovic et al. 2002). Furthermore, HSE-linked ROS are mainly generated due to the activity of microglial nicotinamide adenine dinucleotide phosphate oxidase family enzymes (Bedard and Krause 2007; Hu et al. 2011).

Recent studies have indicated that ROS affect TJ proteins via the following mechanisms: ROS induction of TJ proteins phosphorylation, decreased TJ proteins expression, and induced protein redistribution. Suggesting one potential mechanism for this, the phosphorylation states of TJ proteins regulate their association with the cell membrane (Ozaki et al. 2000; Yamamoto et al. 2008). Claudins and occludin bind to the cytoplasmic C-terminal domain of the actin cytoskeleton in ECs via accessory proteins (ZO-1, ZO-2, and ZO-3). As the phosphorylation status of proteins alters their interactions with transmembrane proteins and the actin cytoskeleton, change to the structure of ECs can indirectly influence ECs' barrier functions (Fanning et al. 1998).

A number of phosphorylation sites have been identified on serine and threonine residues of TJ proteins (Elias et al. 2008; Hirase et al. 2001). Previous experiments have shown that ROS stimulates RhoA/RhoK activation in human immunodeficiency virus-1 encephalitis mice. This leads to the phosphorylation of claudin-5 and occludin and contributes to a reduction in BBB tightness (Yamamoto et al. 2008). In addition, pro-inflammatory cytokines or leukocytes can also activate RhoA and Rac1 via binding to adhesion molecules on ECs, such as ICAM-1. As explained above, this in turn leads to increased leukocyte adhesion and the widening of intercellular gaps, allowing for leukocyte extravasation and thus indirectly altering BBB permeability (van Wetering et al. 2003). The specific phosphorylation mechanisms of these proteins are unclear in HSE.

ROS have also been implicated in the induction of MMP expression via ERK/JNK activation and NF-κB pathways in vivo and in vitro (Hsieh et al. 2010). Given this, ROS may lead to the degradation of TJs and indirectly cause BBB dysfunction via the proteolytic activity of MMPs. Furthermore, ROS can alter the distribution of TJ proteins and induce rearrangements of the actin cytoskeleton via the RhoA/PI3K/PKB signaling pathway. This can in turn change the integrity and permeability of the BBB (Schreibelt et al. 2007).

In summary, ROS contributes to BBB disruption via various mechanisms including TJ protein phosphorylation and the cleavage and redistribution of TJ proteins. ROS may also lead to rearrangement of the actin cytoskeleton and promote EC contractility, resulting in the enlargement of intercellular spaces. Nevertheless, the specific mechanisms underlying the effects of ROS on TJ functions in HSE remain unknown and require further exploration.

MCP-1

MCP-1 (also known as CCL2) is a major chemokine involved in CNS inflammation. MCP-1 was initially recognized for its pivotal role in regulating the migration and activation of specific leukocyte subpopulations in both physiological and pathological contexts (Mantovani 1999). MCP-1 levels have been found to increase with HSV-1 infection (Lima et al. 2010). It has also been reported that the C-C chemokine receptor type 2 (CCR2), which is a receptor for MCP-1, is primarily expressed by neurons, astrocytes, and, particularly, microglia across various regions of the human brain (Banisadr et al. 2002).

MCP-1 is involved in the regulation of the permeability and integrity of the BBB via multiple mechanisms. First, the MCP-1/CCR2 pathway has been shown to modulate the infiltration of leukocytes into multiple types of inflamed tissues including the brain, where they play a beneficial or pathologic role depending on the lesion type. Second, recent evidence indicates that MCP-1 can compromise the integrity of the BBB by redistributing TJs and rearranging the ECs actin cytoskeleton (Stamatovic et al. 2003). Previous studies have demonstrated that MCP-1 can activate ROCK and PKC (especially PKCα) by binding to the receptor CCR2. ROCK stimulates the phosphorylation of myosin light chain phosphatase, leading to increased actin-myosin interactions and stronger actin-myosin contraction in ECs (Garcia et al. 1995; Shen et al. 2006). This EC contraction leads to BBB disruptions by causing ZO-1 to move away from TJs (Stamatovic et al. 2006). A lack of CCR2 expression has been reported to prevent disruptions of the BBB. This strongly supports the idea

that MCP-1 mediates leakage of the BBB via the MCP-1/CCR2 pathway. Furthermore, MCP-1 can be activated by the release of IL-1β and TNF-α. Activated microglia can further release large quantities of cytokines, such as IL-1β and TNF-α, which stimulate the expression of CCR2. We contend that the MCP-1/CCR2 pathway may thus underlie the compromised integrity of the BBB in HSE.

Alterations in Astrocytes in Herpes Simplex Encephalitis

Astrocytes are necessary components of the BBB, with their structure and function playing vital roles in the healthy BBB. Minor changes to astrocytes can also lead to dysfunction of the BBB, including alterations in aquaporin 4 (AQP4), astrogliosis, cell apoptosis, and molecules released by astrocytes. These factors can influence the normal permeability and integrity of the BBB (Fig. 4).

Aquaporin 4

AQP4, which is mainly expressed in astrocytic endfeet, is a water-selective membrane transport protein involved in the translocation of water across the BBB. AQP4 regulates water balance in the brain, glial scarring, and neuroinflammation (Jung et al. 1994), and is altered in many CNS diseases, such as amyotrophic lateral sclerosis (ALS), neuromyelitis optica (NMO), and stroke (Bataveljić et al. 2012; Pirici et al. 2018; Uchida et al. 2017). First, AQP4 is closely associated with brain edema, which is the excess accumulation of fluid in the intracellular or extracellular regions of the brain, including cytotoxic edema and vasogenic edema. AQP4-deficient mice

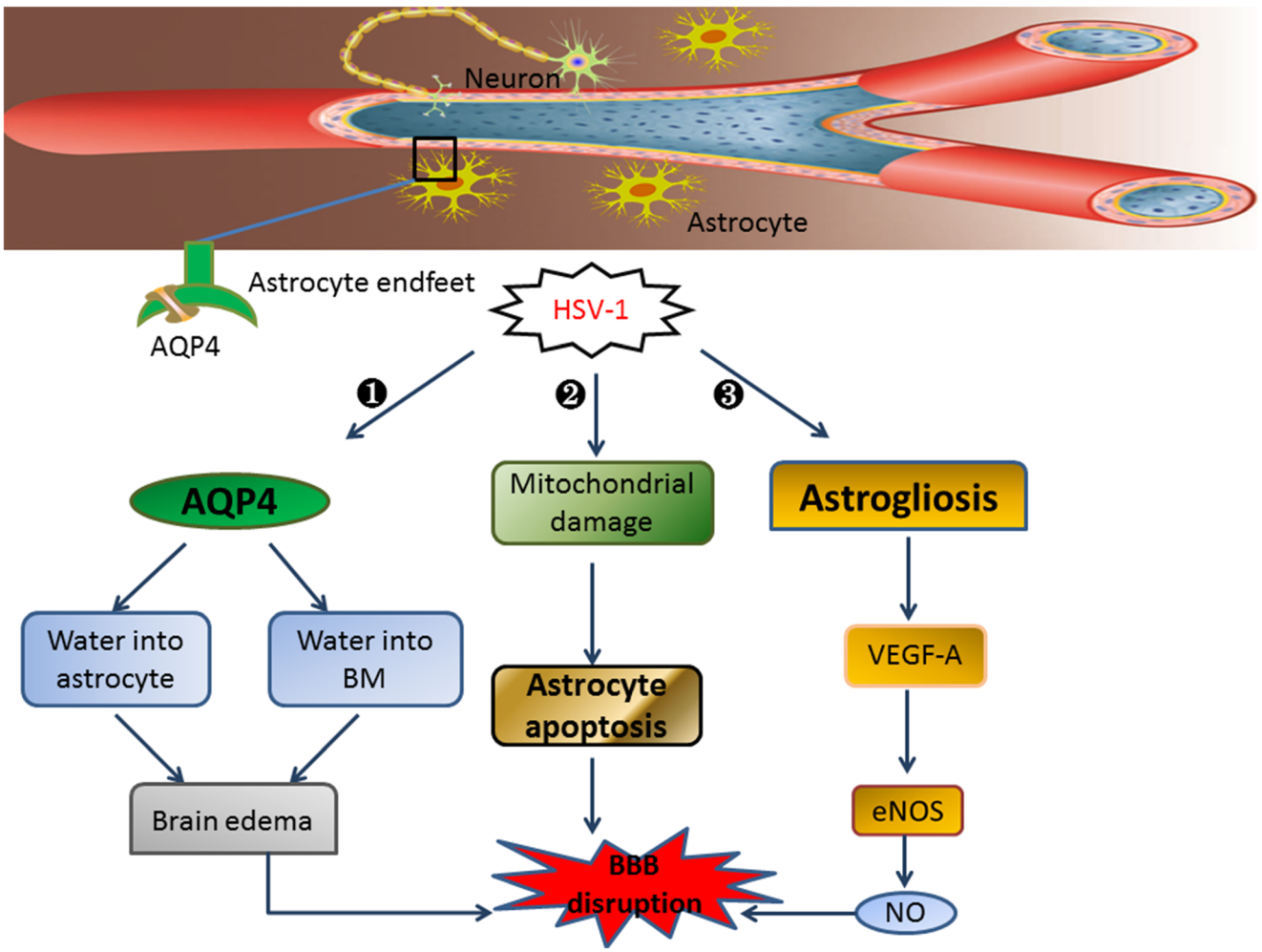

Fig. 4 Alterations to astrocytes due to herpes simplex encephalitis. 1) AQP4: Altered expression of AQP4 after HSV-1 infection. This may promote the movement of water into astrocytes and the BM, causing brain edema, which indirectly leads to BBB disruptions. 2) Apoptosis: HSV-1 infection leads to mitochondrial damage in astrocytes, which results in astrocytic apoptosis and BBB breakdown. 3) Astrogliosis: Astrocytes can be activated after HSV-1 infection, which may lead to astrogliosis. Activated astrocytes secrete many immune factors, including VEGF-A, which stimulates robust NO release by eNOS and thus induces BBB disruption, as depicted in Fig. 2

have been found to exhibit less water accumulation in brain tissues during acute water intoxication and early cerebral ischemia, two cytotoxic edema models (Manley et al. 2000). However, in a vasogenic edema model, wild type mice exhibit elevated water retention in the brain as opposed to AQP4-deficient mice (Papadopoulos and Verkman 2005). This suggests that the role of AQP4 in regulating brain edema is complex, as it is involved in both the formation of cytotoxic edema as well as the elimination of vasogenic edema. Edema is further associated with many different disease mechanisms, rendering it difficult to determine a precise role for AQP4 across these etiologies. However, overexpression of AQP4 leads to increased BBB permeability and thus increased facilitation of water passage into astrocytes, cellular swelling, and BM disruptions. This, in turn, results in disruptions to the BM and elevated intracranial pressure, causing secondary brain damage.

Recent work has shown that AQP4 can also contribute to cytotoxic edema in a rat model of intracerebral hemorrhage, while inhibition of AQP4 alleviates brain edema (Yang et al. 2016). In HSE, brain edematous space-occupying lesions are well-known phenomena (Schmutzhard 2001) and edema is an important factor leading to different neurological sequelae and a high rate of mortality following treatment with an antiviral medication. In vivo studies have revealed that the expression of AQP4 is downregulated in the acute phase of HSE (within 7 days of infection), echoing similar findings from the traumatic brain injury study. This may be a protective mechanism, limiting further glial cell swelling (Kiening et al. 2002). However, in the chronic phrase of an HSE mouse model (after 6 months), the expression of AQP4 is upregulated, potentially increasing permeability to water, leading to a more serious brain edema in vivo (Torres et al. 2007). Cranial magnetic resonance imaging (MRI) of patients with no clinical symptoms, as well as those resulting from use of a mouse model, both exhibit chronic structure damages (Meyding-Lamade et al. 1999a, b). While the expression of AQP4 and its specific roles in HSE patients remain elusive.

Suggesting a potential etiological mechanism for increased BBB permeability following HSE, previous studies have shown that ROS induces the upregulation of AQP4 in neocortical astrocytes in rats via the p38/mitogen-activated protein kinase (MAPK) pathway (Rosenberger et al. 2001). ROS levels are also increased in HSE, potentially leading to the upregulation of AQP4 expression and further brain edema in HSE. Taken together, this suggests that the inhibition of AQP4 may be a promising therapeutic target for the treatment of HSV-1 infection. Furthermore, upregulation of AQP4 in astrocytic endfeet may increase the permeability of the BBB, thus leading to brain edema.

Apoptosis of Astrocytes

HSV-1 can infect astrocytes and neurons following the administration of virus proteins, such as gh625 (Galdiero et al. 2015). As in microglia, astrocytes play a vital role in protecting the brain against pathogens by secreting immune factors (Furr et al. 2011). Apoptosis due to HSE can lead to the death of neurons and glia, including microglia and astrocytes (Aravalli et al. 2006). Apoptosis and necrosis are two critical defense mechanisms that contribute to the elimination of HSV-1-infected cells. In addition, apoptosis may be considered to be a protective strategy that limits viral replication and spread. Previous studies have reported that astrocytes, which are a cellular component of the BBB, undergo apoptosis due to mitochondrial dysfunction in HSE. Two apoptotic pathways have been identified in this dysfunction—extrinsic and intrinsic (Chu et al. 2014).

Mitochondria play an important role in the intrinsic pathway by releasing cytochrome c into the cytosol from the mitochondrial inter-membrane space (Polster and Fiskum 2004). Additionally, mitochondria are necessary for energy production and cell survival (DiMauro and Davidzon 2009). Therefore, damage to mitochondria may contribute to the pathogenic progression of HSE, especially given damage to the BBB, which leads to astrocyte apoptosis. Using non-neuronal or transformed cell lines, researchers have shown that HSV-1 can interact with mitochondria. Specifically, viral proteins can migrate into the mitochondria and affect its function (Derakhshan 2006; Duguay and Smiley 2013; Murata et al. 2000; Saffran et al. 2007). Based on these findings, we can conclude that mitochondrial damage leads to the apoptosis of astrocytes, which in turn may disrupt the BBB during HSV-1 infection.

Astrogliosis

Astrocytes respond to a variety of brain insults including infection, inflammation, ischemia, and neurodegeneration, via a process termed astrogliosis (Burda and Sofroniew 2014; Maragakis and Rothstein 2006). Astrogliosis refers to a process that involves morphological and molecular changes, including hypertrophy, increased expression of proteins, such as glial fibrillary acid protein (GFAP), and glia scar formation in severe circumstances (Alvarez et al. 2013; Sofroniew 2009). In general, increased expression of GFAP is a marker of astrogliosis, which has been observed several days after HSV-1 infection (Kumaraswamy et al. 2006). Similarly, Armien and colleagues reported significant astrogliosis and dramatically increased glia scar formation in brain regions damaged by HSV-1 infection where persistent inflammation was also observed. These effects are present both acutely (2 days post-infection), and more chronically (30–60 days post-infection) (Armien et al. 2010).

Today, the role of astrogliosis in the course of HSE remains the source of some debate. Some studies have reported that astrogliosis exerts beneficial effects, including on wound closure, neuronal protection, and BBB repair (Sofroniew 2005).

However, others have shown that astrogliosis may be harmful, as in the context of inflammation (Sofroniew 2015; Sofroniew and Vinters 2010). For instance, Japanese encephalitis virus (JEV) infection leads to astrogliosis and increased BBB permeability and promotes leukocyte invasion of the CNS, leading to a more robust neuroimmune response. Some have also recently proposed that astrogliosis may lead to increased release of soluble factors, such as VEGF-A (Argaw et al. 2012), as reactive astrocytes release VEGF-A in MS and EAE. This can in turn lead to BBB breakdown via eNOS-dependent mechanisms, which in turn results in the downregulation of claudin-5 and occludin expression (Argaw et al. 2006; Proescholdt et al. 2002). Greater elucidation of the specific roles of astrogliosis in HSE, however, requires further investigation.

Based on the findings discussed here, we conclude that astrocytes are involved in BBB disruption via altered AQP4 expression, apoptosis, and astrogliosis.

Alterations in Pericytes

Pericytes are adjacent to capillaries and share a common BM with ECs. Pericytes infected with JEV-1 release biologically active molecules that activate the ubiquitin proteasome, which is involved in the degradation of >80% of proteins in the human body. This leads to the degradation of ZO-1 and disruption of the integrity of the endothelial barrier in cultured ECs. In this study, changes in ECs were accompanied by the activation of IL-6-induced ubiquitin-proteasome-dependent degradation mechanisms (Chen et al. 2014). Activated microglia release IL-6 during HSV-1 infection, raising the question of whether pericytes promote ZO-1 degradation via the same mechanism as in HSV-1 infection. In addition, pericytes are the most sensitive cells to TNF-α in the BBB and release MMP-9 in response to insult (Fuyuko Takata and Eriko Harada 2011). Thus, pericytes promote BBB disruption in neuroinflammatory diseases due to the proteolytic functions of MMP-9. Indeed, TNF-α induces the release of MMP-9 from pericytes via the actions of MAPK and PI3K. The precise role of pericytes in the breakdown of the BBB in HSE, however, remains unclear. To date, no studies have directly revealed that pericytes are involved in BBB disruptions with HSE. Studies of JEV infection raise the possibility that pericytes are involved in the pathogenesis of BBB breakdown. However, the mechanisms underlying these outcomes are unclear and thus require further research.

Alterations in the Basement Membrane

The BM is primarily composed of structural proteins, such as type IV collagen, laminin, and fibronectin, but also contains cell adhesion molecules and immobilized signaling proteins. It is well known that ECM proteins, such as type IV collagen, laminin, and fibronectin, are substrates of MMPs, especially MMP2 and MMP9, which are described above. These MMPs can cleave ECM proteins and lead to compromised BBB integrity (Zhang et al. 2016).

Other Factors

Many other factors may lead to disruptions in the integrity of the BBB in HSE, including VEGF and the Golgi apparatus (GA).

Vascular Endothelial Growth Factor (VEGF)

VEGF was originally discovered as a vascular permeability factor, required for normal development of the embryonic vascular system. VEGF can influence the normal barrier function of the BBB by binding to the VEGF receptor. In herpes simplex keratitis, the area infected by HSV is proportional to the increase in VEGF expression.

VEGF is implicated in BBB damage via various mechanisms. In EAE, astrocyte-derived VEGF can breakdown the BBB by altering claudin-5 and occludin (Argaw et al. 2009). In addition, one study reported that VEGF increased the monolayer permeability of endothelial cells via reductions in ZO-1 and occludin expression (Zhang et al. 2015). Furthermore, VEGF promotes NO production by inducing eNOS and iNOS expression in vascular endothelial cells, leading to increased BBB permeability (Fukumura et al. 2001). VEGF inhibition can conversely alleviate BBB damage via modulation of MMPs expression in the early stages of an ischemic stroke (Zhang et al. 2017). In JEV, astrocyte-derived VEGF leads to the degradation of ZO-1 and results in BBB disruptions (Chang et al. 2015). Therefore, we speculate that VEGF plays a potentially critical role on the BBB disruption that occurs with HSE. However, while it is known that the expression of VEGF is upregulated in HSE, the mechanisms by which VEGF affects BBB function remain unknown.

Golgi Apparatus

Involved in the replication of HSV-1 in cells and the formation of viral packaging and transport vesicles, the GA is an important organelle necessary for protein synthesis, modulation, and secretion. Trans-Golgi networks form nucleocapsids by budding and forming vesicles responsible for viral envelopment and transport (Mettenleiter 2004). For instance, prior work found coated HSV-1 virions in the lateral pool of the GA (Leuzinger et al. 2005).

The structure of the GA also influences its function. In addition, at different time points after infection, the GA's structure significantly transforms from an expanded membrane to a fragmented one. In the later stages of an infection,

the intact structure of the GA completely disappears (Sutter et al. 2012). In some clinical conditions, such as ischemic stroke, the GA undergoes robust changes and has an important role in pathogenesis (Li et al. 2016).

The GA may be involved in BBB damage following HSV-1 infection via two mechanisms. First, loss of the normal GA structure prevents the normal production of proteins, such as receptors and ion channels in ECs, astrocytes, and TJs. This can lead to compromised BBB barrier function. Second, the GA is a vital site of calcium ion storage and as such, its fragmentation leads to increased cytoplasmic Ca^{2+} release and stimulates eNOS activation, which modulates downstream effectors, such as NO and VEGF. These effectors may then lead to BBB breakdown, as described above (Ko et al. 2015b).

In addition to its role in viral infection, our team has reported on the extensive relationships between the GA and neurological diseases (Fan et al. 2008)—in particular, between the GA and the BBB (Deng et al. 2017). For instance, Golgi phosphoprotein 3 (GOLPH3), a peripheral membrane protein belonging to the trans-Golgi network, which contributes to protection of the GA, has been shown to be up-regulated at the protein level by oxidative stress (Li et al. 2014; You et al. 2014). Furthermore, GOLPH3 promotes the expression and activity of MMP2 and MMP9 (Li et al. 2015; Wang et al. 2015a, b). GOLPH3 and eNOS also co-localize at the GA (Sangwung et al. 2012), indicating that disruption to GOLPH3 after HSV-1 infection may contribute to disruptions in the BBB. In summary, we speculate that the GA is a vital factor in virally-induced decrements to the BBB.

Conclusion

It is widely accepted that HSE results in disruptions to the BBB, though few studies have characterized the mechanisms that may underlie this. ECs, TJs, astrocytes, pericytes, and the BM are all components of the BBB that demonstrate structural and functional changes following HSV-1 infection, which can alter the integrity and permeability of the BBB and aggravate brain damage. Microglia are not an anatomical component of the BBB, though they participate in BBB dysfunction in distinct ways via the secretion of potent pro- and anti-inflammatory cytokines. Therefore, understanding how the functioning of microglia is disrupted following an HSV-1 infection is a key question for future investigation. Meanwhile, there are still various unclear mechanisms about BBB disruption and need further explore. The review undertaken here provides critical insights into the components which underlie BBB integrity and dysfunction in HSE, and may thus provide a guide for developing novel, safe, and efficacious therapeutic approaches to its treatment.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Abbreviations TJs, tight junctions; AJ, adhesion junction; BM, basal membrane; BBB, blood-brain barrier; CNS, central nervous system; EAE, experimental autoimmune encephalomyelitis; EC, endothelial cells; ECM, extracellular molecules; GA, Golgi apparatus; HSE, Herpes simplex encephalitis; HSV-1, herpes simplex virus 1; ICAM, intracellular adhesion molecule; IFN, interferon; IL-1β, interleukin 1-beta; iNOS, inducible nitric oxide synthase; MMP, Membrane metalloprotease; NF-κB, nuclear factor kappa B; PKC, protein kinase C; TEER, transendothelial electric resistance; TNF-α, tumor necrosis factor alpha; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; ZO, zonula occluden.

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